UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/407,430	09/29/1999	HOWARD J. WORMAN	0575/54805	2750

7590 01/26/2004

JOHN P WHITE
COOPER & DUNHAM LLP
1185 AVENUE OF THE AMERICAS
NEW YORK, NY 10036

EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 01/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/407,430	WORMAN ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication app ars on the cover sh et with the correspond nce addr ss --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 27 October 2003.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 101-106 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 101-106 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

New claims 101-106 are pending in the present application. New claims 101-106 are identical to previously rejected claims 44-49, respectively, which are now cancelled.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New claims 101-106 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the same reasons already set forth in the previous Final-Rejection Office Action mailed 12/23/02 (pages 3-10).

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

Claims 101-106 are drawn to a method of inhibiting attachment of hepatitis C virus onto a cell, which comprises contacting the cell with an effective amount of an E_0 protein having amino acids 1-120 of SEQ ID NO:1 to the subject, wherein the E_0 protein is capable of inhibiting the attachment of hepatitis C virus onto cells by specifically binding to the hepatitis C virus envelope E2 protein; the same method with various limitation in the dependent claims.

The specification teaches by exemplification that using the yeast two hybrid assay, two clones encoding a portion of a protein were selected from a library of human liver Matchmaker cDNA for interacting with a portion of hepatitis C virus E2 lacking its most hydrophobic, carboxyl terminal domain. The sequence of the encoded portion of a

protein, referred to as E_o protein, has the amino acid sequence of SEQ ID NO: 1. Furthermore, the specification teaches that the encoded amino acid sequence containing amino acid residues 1-120 of SEQ ID NO:1 (or E_o1 protein) is also capable of binding to the portion of hepatitis C virus E2 as does the E_o protein of SEQ ID NO:1, although at a relatively weaker binding affinity (See specification, pages 18-20).

The above evidence has been noted and considered. However, the evidence is not reasonably extrapolated to the instant claimed invention which is drawn to a method of inhibiting attachment of hepatitis C virus onto a cell in a subject using an effective amount of E_o protein having amino acids 1-120 of SEQ ID NO:1.

When read in light of the specification, the sole purpose for the claimed method is to attain therapeutic effects against hepatitis C infection in a subject through the use of an effective amount of an E_o protein having amino acids 1-120 of SEQ ID NO:1 to inhibit the attachment of hepatitis C virus onto a cell. The instant specification is not enabled for the claimed invention because it fails to provide any guidance regarding the use of any effective amount of an E_o protein having amino acids 1-120 of SEQ ID NO:1 to treat or prevent hepatitis C infection in any subject or to prevent the attachment of hepatitis C virus onto a cell in a subject. The specification fails to teach or demonstrate a correlation or a nexus between the binding interaction of the E_o protein having SEQ ID NO:1 and the E_o1 proteins with a portion of the hepatitis C virus E2 envelope protein observed via the yeast two hybrid assay with any of the therapeutic effects contemplated by the claimed invention which comprise the inhibition of HCV replication, stopping or delaying the progression of liver disease in a subject or to prevent

attachment of hepatitis C virus onto a cell in a subject. Apart from the yeast two hybrid assay system, there is no evidence of record indicating or suggesting that a similar interaction between E_o or E_o1 protein with a portion of the hepatitis C virus E2 envelope protein would also occur in other non-yeast biological systems, let alone for attaining the desired results contemplated by Applicants. Rosa et al. (Proc. Natl. Acad. Sci. 93:1759-1763, 1996; IDS) have reported that in contrast to E2 protein expressed in mammalian cells, E2 protein expressed in yeast or insect cells are not capable of binding to human cells (see Fig. 1), nor do they elicit neutralizing antibodies to protect chimpanzees from primary infection by an homologous hepatitis C isolate (page 1761, col. 2, top of first full paragraph). Thus, it is unclear about the significance of the interaction between E_o or E_o1 protein with a portion of a hepatitis C virus E2 envelope protein solely in yeasts as reported in this application to the desired results contemplated by Applicants to be attained in a subject. Furthermore, in a review on the yeast two-hybrid system (Current Opinion in Biotechnology 6:59-64, 1995), Luban et al. have noted that a major problem associated with two-hybrid screens is the appearance of false-positives inherent in any transcriptional readout, and strong evidence for a direct interaction between the proteins should be provided in a biochemical assay, preferably one should show that the two proteins co-precipitate in their native context (page 62, col. 1, second full paragraph). Luban et al. further stated "The last issue, which is usually the most difficult aspect of working with the two hybrid system, is that one must demonstrate the functional significance of the protein-protein interaction that one has discovered" (page 62, col. 1, top of the third full paragraph). Since the prior art at the filing date of the present

application does not provide any guidance regarding to the use of any effective amount of E_o or E_o1 protein to attain the results contemplated by Applicants in a subject, it is incumbent upon the instant specification to do so. Particularly, at the filing date of the present application, standard treatments for patients infected with hepatitis C include therapies using recombinant alpha interferon alone or in combination with the nucleoside analogue Ribavirin, whose actions are not mediated via inhibiting the attachment of hepatitis C virus onto cells (Gish, Seminars in liver disease 19 (S1): 35-47, 1999; Cited previously). Since the physiological art is recognized as unpredictable (MPEP 2164.03), and as set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictagle factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

Accordingly, with the lack of guidance provided by the instant specification, it would have required undue experimentation for one skilled in the art to make and use the instant claimed invention.

At the filing date of the present application, it was already known in the art that other polypeptides such as the CD81 protein (Abrignani et al., WO 99/18198; see page 2, lines 18-25; Cited previously), annexin V, tubulin, apolipoprotein B (Maertens et al., WO 99/24054; see abstract; Cited previously), as well as endogenous host proteins such as the chaperone protein calnexin and lactoferrin are also capable of binding at least to the hepatitis C virus envelope protein E2 (Maertens et al., WO 99/24054; page

2, lines 12-29). However, the potential therapeutic values of these proteins for treating HCV infection in a subject remain to be determined or investigated because the mechanism by which HCV enters target cells remains unknown (Flint et al., J. Virol. 73:6782-67900, 1999; page 6782, column 2, last three lines). Flint et al. stated that "Clearly, it will be important to demonstrate whether CD81, either alone or with additional factors, can function as the HCV receptor in allowing pseudotyped virus-cell attachment and entry. Since CD81 is so widely expressed, it is unlikely to be the sole factor determining HCV liver tropism" (page 6789, column 1 lines 1-6). Since it is unclear how hepatitis C virus enters target cells in the art at the filing date of the present application, then how the simple binding of E_o or E_o1 protein with a portion of a hepatitis C virus E2 envelope protein in a yeast two-hybrid assay can be reasonably extrapolated to inhibiting attachment of HCV virus onto any cell in a subject as claimed to attain therapeutic effects contemplated by Applicants. Additionally, even suppose that the simple binding of any protein with the E2 envelope protein is a reasonable correlation for preventing attachment of HCV virus onto cells in a subject, and thereby treating or preventing HCV infection, then why CD81, annexin V, tubulin, apolipoprotein B as well as calnexin and lactoferrin have not been routinely used in the treatment or therapy for patients infected with HCV? With the absence of sufficient guidance provided by the instant specification, particularly with the lack of any *in vivo* example (part of guidance), it would have required undue experimentation for a skilled artisan to make and use the presently claimed invention.

With respect to the use of an E_o protein having amino acids 1-120 of SEQ ID NO: 1 in the method as claimed, it is unclear whether the E_o protein is capable of exhibiting an effective binding affinity for the full-length E2 envelope protein presented on the surface of the hepatitis C virus, usually in complexes with other viral envelope components, such as the E1 envelope protein, such that it can disrupt such complexes and thereby preventing the attachment of hepatitis C virus onto any cell or preventing or treating hepatitis C virus infection in a subject. Gish noted that the standard management of chronic HCV infection is complicated by various factors, including: the rapid mutation rate of the HCV genome, particularly the hypervariable region, the lack of neutralizing antibodies to HCV gene products, and the lack of sequence homology (less than 72%) among various subtypes of HCV (page 36, column 1, first full paragraph, line 8 continues to the first paragraph on column 2). It is also thought that the binding of E2 to target cells mostly involves the highly variable amino terminus of E2, the hypervariable region I (Maertens et al., WO 99/24054; page 2, lines 12-17). As such, it is unclear whether E_o or E_o1 protein, is capable of binding efficiently *in vivo* to the highly variable region of E2 in any HCV subtype such that it can inhibit the attachment of HCV onto any cell and thereby treating and preventing HCV infection in a subject. Therefore, given the complete lack of guidance provided by the instant specification regarding to the effective *in vivo* use for any E_o protein that is capable of inhibiting the attachment of hepatitis C virus onto cell so as to treat and prevent HCV infection in a subject, it would have required undue experimentation for a skilled artisan to make and use the claimed invention.

The instant claims encompass any route of administering the E_o protein into a subject to inhibit attachment of hepatitis C virus onto a cell in a subject. However, the instant specification fails to provide any relevant information regarding to the *in vivo* stability of the E_o protein utilized or how to overcome random degradation of the administered E_o protein in a treated host and more importantly how to target the E_o protein to a desired tissue or organ in an effective amount by any means of delivery such that any therapeutic effects (treatment and prevention) or preventing attachment of hepatitis C virus onto any cell in a subject as contemplated by Applicants could be attained. Again, in the absence of any guidance provided by the instant specification, it would have required undue experimentation for a skilled artisan to make and use the instant claimed invention.

Accordingly, due to the lack of guidance provided by the specification regarding to the issues set forth above, the state of the art on treatment of hepatitis C at the effective filing date of the present application, the unpredictability of the physiological art, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instant claimed invention.

Responses to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on 10/27/03 (pages 7-8) have been fully considered.

Applicants argue mainly that the use of a yeast two-hybrid screen with a portion of the E2 protein to determine the binding to a human E2 protein in the Boner et al.

reference (abstract provided by Applicants) as recent as 2002 indicates that the concerns raised by Rosa et al. and Luban et al. do not accurate reflect the state of the art. Therefore, Applicants contend that claims 101-106 are enabled by the present specification.

Applicants' arguments are not found persuasive because the Boner et al. reference is not relevant to the presently claimed invention. The cited reference concerns the identification of cellular interacting partners for HPV 16 E2 protein using a yeast two-hybrid screening. Human papillomaviruses (HPV) are nonenveloped DNA viruses that infect epithelial cells resulting in a range of lesions from benign skin and genital warts (condyloma acuminata) and epidermodysplasia verruciformis (EV) to respiratory or laryngeal papillomatosis and cervical carcinoma, whereas HCV is a positive single stranded RNA virus and a member of the Flavivaridae family that causes chronic liver disease, cirrhosis and hepatocellular carcinoma. HPV 16 E2 is not an envelope protein, whereas HCV E2 protein is. Therefore, the identification of cellular interacting partners for HPV 16 E2 protein is not relevant to the ability of an E_0 protein which is identified via a yeast two-hybrid screen to inhibit attachment of hepatitis C virus onto a cell by binding to HCV E2 protein. Particularly, the significance of the interaction between E_o or E_o1 protein with a portion of a hepatitis C virus E2 envelope protein solely in yeasts as reported in this application is unclear and not reasonably correlated to the desired results contemplated by Applicants because Rosa et al. (Proc. Natl. Acad. Sci. 93:1759-1763, 1996; IDS) have already reported that in contrast to E2 protein expressed in mammalian cells, E2 protein expressed in yeast or insect cells are not

capable of binding to human cells (see Fig. 1), nor do they elicit neutralizing antibodies to protect chimpanzees from primary infection by an homologous hepatitis C isolate (page 1761, col. 2, top of first full paragraph). Additionally, Applicants' truncated $E2_{384-661}$ expressed in the yeast two hybrid assay system is not a physiological form of E2 protein that would be present on the surface of HCV, because Applicants' truncated E2 protein is fused with the GAL4 DNA binding domain, and that it is not even in the non-covalent E1-E2 complex, a functional unit that mediates entry of HCV into target cells (Yi et al., Virology 231:119-129, 1997; Cited by Applicants previously in Exhibit 17). Moreover, in a review on the yeast two-hybrid system (Current Opinion in Biotechnology 6:59-64, 1995), Luban et al. have noted that a major problem associated with two-hybrid screens is the appearance of false-positives inherent in any transcriptional readout, and strong evidence for a direct interaction between the proteins should be provided in a biochemical assay, preferably one should show that the two proteins co-precipitate in their native context (page 62, col. 1, second full paragraph). Luban et al. further stated "The last issue, which is usually the most difficult aspect of working with the two hybrid system, is that one must demonstrate the functional significance of the protein-protein interaction that one has discovered" (page 62, col. 1, top of the third full paragraph). Lastly, there is no evidence of record (*in vitro* or *in vivo*) or in the prior art at the filing date of the present application indicating that the E_o protein of the present invention can disrupt the E1 and E2 heteromeric complex (already formed complex) that is thought to be necessary for HCV virus binding and entry to the cells as taught by Yi et al. and asserted by Applicants.

Accordingly, the claims are rejected for the reasons set forth above.

Conclusions

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (571) 272-0767, or SPE, Remy Yucel, Ph.D., at (571) 272-0781.

Quang Nguyen, Ph.D.

DAVID GUZO
PRIMARY EXAMINER